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Research paper

Frequency of bleeding and thromboembolism in patients with atrial fibrillation on warfarin at a tertiary care hospital in Sri Lanka

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Abstract

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, significantly increases stroke risk with approximately one in five strokes attributed to AF[1,2,3]. Oral anticoagulation, primarily with warfarin, is crucial for AF management, especially in valvular AF where it remains the drug of choice. However, warfarin's narrow therapeutic range poses a significant bleeding risk, with intracranial haemorrhage being the most serious complication. Time in Therapeutic Range (TTR) is a key metric for assessing anticoagulation efficacy and safety, with TTR values above 70% correlating with better outcomes. This is a retrospective descriptive cross-sectional study aimed to determine the frequency of bleeding and thromboembolism in AF patients on warfarin over six months at the National Hospital of Sri Lanka (NHSL), describe their demographic profile, determine predicted bleeding risk using the HAS-BLED score, and evaluate anticoagulation effectiveness via TTR. The cohort had a mean age of 62.41 years, with a female predominance (73%). Seventeen percent of patients experienced at least one bleeding episode during follow-up, with 4% being major bleeds. All major haemorrhages occurred with supratherapeutic INR values (INR >5), although no significant correlation was found between bleeding type and INR values (p=0.187). No significant correlation between HAS-BLED score and bleeding (p=0.156), but 3 out of 4 major bleeds were of high-risk HAS-BLED category. Twenty-six percent had stroke/ transient ischemic attack (TIA) during follow-up; only 1 had a stroke in the past 3 months who had a subtherapeutic INR at the time. There was no correlation between stroke/ TIA/ thromboembolism and CHA2DS2VASc score (p=0.36). Only 45.435% of the patients had INR values within the therapeutic range and 62% of patients had a TTR below 60%. There was no significant association between TTR and either bleeding or thrombotic episodes. The study concluded that warfarin can be safely used in this setting for AF patients, but the observed lack of predictive power for HAS-BLED and CHA2DS2VASc scores, alongside suboptimal TTR, highlights the need for further larger-scale, multicenter studies.

Introduction

Atrial fibrillation (AF) is recognized as the most prevalent sustained cardiac arrhythmia requiring treatment, with its incidence increasing with age. AF significantly elevates the risk of stroke, with approximately 20% of all strokes being attributable to this condition. Given this substantial risk, prophylactic oral anticoagulation is a cornerstone in the management of AF, particularly for patients with valvular heart disease or a CHA2DS2VASc score of 2 or higher.

Historically, warfarin, a vitamin K antagonist (VKA), has been the primary anticoagulant for stroke prevention in AF. Warfarin works by inhibiting the vitamin K epoxide reductase complex, thereby depleting reduced vitamin K necessary for the gamma carboxylation of vitamin K-dependent clotting factors and prolonging prothrombin time. Despite its efficacy, warfarin therapy is challenging

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due to its narrow therapeutic range, necessitating close monitoring of the International Normalized Ratio (INR). The major side effect of warfarin is bleeding, ranging from minor episodes to life-threatening intracranial haemorrhage[4]. To mitigate this, bleeding risk assessment using scores like HAS-BLED is recommended both before initiating and periodically during anticoagulation. While a high HAS-BLED score indicates elevated bleeding risk, the continuous assessment and management of modifiable risk factors are crucial, as stroke risk often warrants ongoing anticoagulation[5,6].

The effectiveness and safety of warfarin are significantly influenced by the intensity of anticoagulation, with higher INR values increasing bleeding risk and lower values elevating thrombosis risk. Time in Therapeutic Range (TTR), calculated using methods like the Rosendaal method, is a key indicator of anticoagulation quality, with TTR values exceeding 70% generally correlating with optimal efficacy and safety. While direct oral anticoagulants (DOACs) have emerged and gained approval for non-valvular AF, warfarin remains the drug of choice for valvular AF[7,8].

Despite the global body of research on warfarin, studies specifically assessing the frequency of bleeding and thromboembolism, particularly concerning TTR, are limited in the Sri Lankan context. A previous Sri Lankan study found no significant relationship between major bleeding events and HAS-BLED score, though labile INR was associated with major bleeding[9]. Therefore, this study aimed to determine the frequency of bleeding and thromboembolism in AF patients on warfarin at a major Sri Lankan hospital, describe their demographic profile, determine predicted bleeding risk using the HAS-BLED score, and assess anticoagulation effectiveness by evaluating TTR. The findings are intended to inform decisions on the effectiveness of warfarin and the potential need for introducing DOACs in government hospitals in Sri Lanka.

Methods

This study employed a retrospective descriptive cross-sectional design to analyze the frequency of bleeding and thromboembolism in patients with atrial fibrillation (AF) on warfarin. The study was conducted at the anticoagulation clinic within the Department of Haematology and the Cardiology Unit of the National Hospital of Sri Lanka (NHSL).

The study population comprised patients with AF who had been on warfarin for more than six months and were followed up at the anticoagulation clinic or cardiology unit of NHSL between October 2020 and October 2021. A sample size of 100 patients was determined using the formula $z^2p(1-p)/d^2$, assuming a 95% confidence level (z=1.96), an expected prevalence (p) of 50% for conservative maximization of sample size and a required precision (d) of 10%. Accounting for a 5% non-respondent rate, the final sample size was rounded to 100. A non-probability consecutive sampling technique was used to recruit all eligible patients until the required sample size was met.

Inclusion criteria for the study were patients with AF on warfarin for over six months from the date of data collection. Exclusion criteria included patients on anticoagulation for indications other than AF and those deemed non-compliant with warfarin therapy (defined for this study as one or more missed doses per week).

Data were collected by the researcher using a pretested, interviewer-administered data collection sheet after obtaining informed written consent from patients in their preferred language (Sinhala, Tamil or English). Relevant details regarding INR values, bleeding episodes, and other risk factors were gathered from both patient interviews (lasting 15-20 minutes during their usual clinic visits) and their clinic records.

Collected data were securely entered into SPSS v23 for analysis. Descriptive statistics were used, with discrete and continuous variables summarized using mean/median, and categorical data presented as percentages and confidence intervals.

The HAS-BLED score was calculated for each patient to predict bleeding risk. One point was assigned for each of the following: hypertension (uncontrolled, systolic blood pressure >160 mmHg), abnormal renal function (dialysis, transplant, or creatinine >2.26 mg/dL), abnormal liver function

(cirrhosis, bilirubin >2x normal, or AST/ ALT/ ALP >3x normal), prior history of stroke, bleeding history or predisposition (prior major haemorrhage, anaemia or severe thrombocytopenia), labile INR (defined as 2 INR values >5, 1 INR value >8, 2 INR values <1.5, or TTR <70%), concomitant drugs (antiplatelets/ NSAIDs), and alcohol use (>14 units/week). Patients were categorized into low risk (total score 0), intermediate risk (total score 1-2) or high risk (total score ≥3).

TTR was calculated using the INOPRO system, which implements the Rosendaal method. This method estimates TTR by assuming a linear variation of INR between consecutive tests and summing the time spent within the therapeutic range over the total observation period.

P-values were calculated where appropriate, with statistical significance defined as a p-value ≤ 0.05. Results were presented using tables, graphs and pie charts.

The study obtained authorization and permission from the Director of NHSL, the Head of the Department of Pathology, NHSL and relevant consultants of the Cardiology Unit. Ethical clearance was granted by the Ethical Review Committee of NHSL before study commencement. Patients received an information sheet in all three languages and informed written consent was obtained prior to data collection. Patient management was not altered and no additional investigations were conducted as a result of participation. Data collection occurred during routine clinic activities, minimizing interference. Patients retained the right to withdraw voluntarily without affecting their future care. All sociodemographic data were collected without individual identifiers to ensure patient confidentiality and study findings are intended for scientific publication.

Results

A total of 100 patients were enrolled in the study. The cohort showed a female predominance (73%) compared to males (27%) (Figure 1). This finding contrasts with male predominance reported in global literature[8] but is consistent with another Sri Lankan study[9]. This result might be affected by the gender distribution of the area because females outnumber males especially in older age groups.

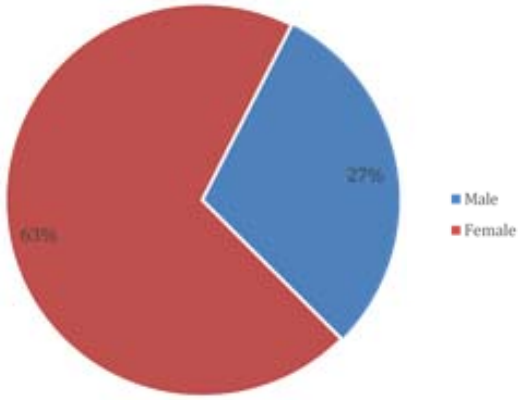

Figure 1. Sex distribution of the subjects in the study.

The mean age of the participants was 62.41 years (median 65 years, range 34-80 years), with 65% of patients being over 60 years and 54% over 65 years (Figure 2). This aligns with the known increase in AF incidence with advancing age[8]. While the mean age was lower than some large international cohorts (e.g., 73.1 years in Germany, 69 years in France[10,11]) it was consistent with previous Sri Lankan data[9].

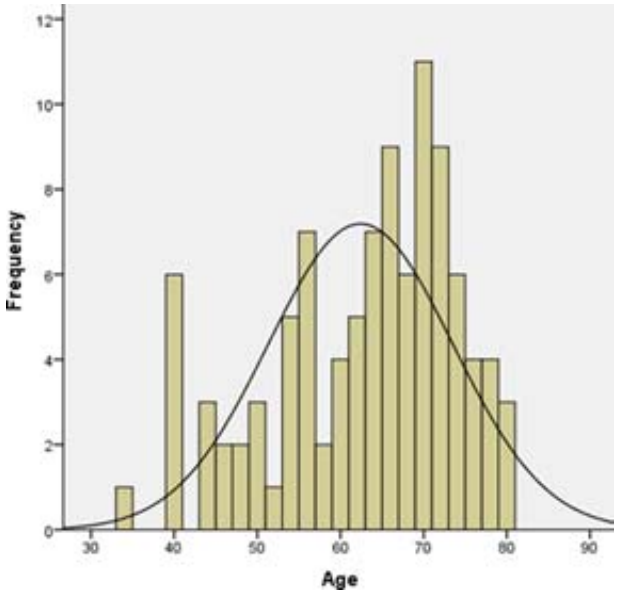

Figure 2. Age distribution of the subjects in the study.

Regarding geographical distribution, 54% of patients were from Colombo or its suburbs, 35% from other areas within the Western province, and 11% from provinces outside the Western province (Figure 3). The mean age at which anticoagulation was initiated was 55.29 years (range 27-79 years). The mean period of clinic follow-up was 7.16 years (median 7 years, range 1-21 years), consistent with other studies at NHSL where a majority of patients were followed for at least five years.

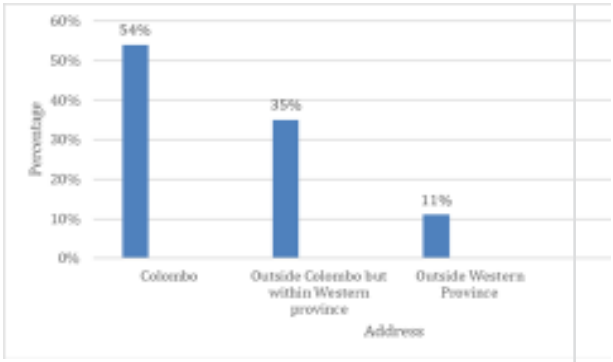

Figure 3. Distribution according to the residence of the subjects in the study.

While on warfarin, out of the 100 patients, 17% experienced at least one bleeding episode during follow-up, with only 3% having a bleeding episode in the last six months. Major bleeding episodes, defined as symptomatic bleeding in critical organs, significant haemoglobin drop (≥2g/dl), or transfusion of ≥2 units of blood, occurred in 4% (4 patients) (Table 1). Minor bleeding episodes occurred in 13% of patients. The observed major bleeding frequency of 4% was higher than a previous Sri Lankan study (2.2%)[9] but lower than some international reports (e.g. 7.1%)[14].

Table 1. Type of bleeding episode

Type of bleeding	Frequency	Percent
No bleeding	83	83.0
Major bleeding episode	4	4.0
Minor bleeding episode	13	13.0
Total	100	100.0

Upon admission with bleeding, 15 out of 17 patients (88.23%) had supratherapeutic INR values, while 2 patients (11.76%) had INR within the therapeutic range. No patients had subtherapeutic INR values on admission with bleeding. The majority (53.3%) with supratherapeutic INR had values between five and eight and 33.3% had INR values greater than eight (Figure 4). All four patients who experienced major bleeding episodes had INR values greater than five on admission even though there was no statistical significance between the type of bleeding episode (major vs. minor) and the INR value on admission (p=0.187). This finding aligns with Breen et al.'s observation that a majority of bleeding events occur with supratherapeutic INR, yet it underscores the complexity of predicting bleeding type solely based on a single INR value at presentation[15].

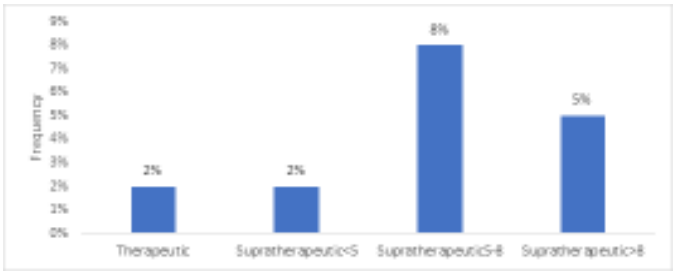

Figure 4. INR values on admission with bleeding.

Regarding HAS-BLED scores, 67% of patients with bleeding were categorized as intermediate risk (scores 1-2), with 34% having a score of 2 and 33% having a score of 1. Seventeen percent were in the high-risk category (score ≥3) and only 16% had a low risk (score 0) (Figure 5). These findings are consistent with a previous Sri Lankan study[9].

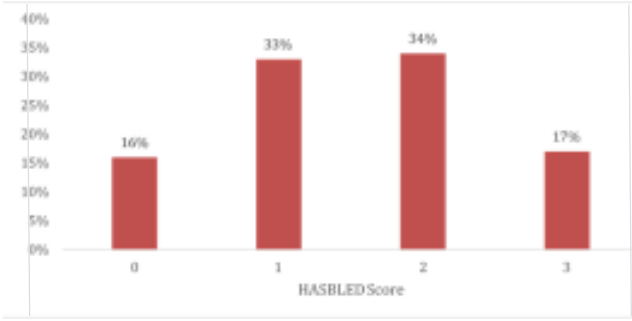

Figure 5. Frequency of bleeding according to the HASBLED score.

No significant association was found between the HAS-BLED score and the occurrence of bleeding episodes overall (p=0.156). However, it is important to note that three out of the four patients who experienced major bleeding episodes were found to be in the high-risk category based on their HAS-BLED scores. This lack of overall significant correlation between HAS-BLED and bleeding events in our study contradicts findings from several international studies that have shown HAS-BLED to be predictive of major bleeding[16,17,18]. Our result is, however, similar to another Sri Lankan study that also found no significant correlation[9]. This discrepancy may be attributed to differences in patient populations, follow-up durations or study designs, emphasizing the need for local validation of such risk scores.

During the follow-up period, 26% (26 patients) experienced a stroke or transient ischemic attack (TIA). Out of them, one patient had a stroke within the most recent three months of follow-up (Table 2) and this occurred when their INR value was subtherapeutic. Other 25 patients who had strokes or TIAs before were not considered for the analysis, as the CHA2DS2VASc score had not been calculated at the time of the stroke or TIA. No significant correlation was identified between the CHA2DS2VASc score and the occurrence of stroke/TIA/ thromboembolism (p=0.36). This finding contrasts with international literature, where CHA2DS2VASc score is widely used and validated for predicting thromboembolic risk in AF patients, while some studies support its utility in identifying low-risk patients[19,20].

The lack of significant association in our cohort, coupled with the absence of comparable Sri Lankan studies, suggests that further local research is needed to understand the applicability of this score in this specific population.

The effectiveness of anticoagulation was assessed by analyzing INR values and TTR. Out of 722 total INR readings, only 45.435% were within the therapeutic range, with 54.57% being out of range (23.82% higher and 30.75% lower than the therapeutic range). Only 38% of patients had their last INR within the therapeutic range. This suboptimal INR control, with over half of the readings out of range, is a critical finding and is consistent with observations from studies in other European countries[23].

When TTR was calculated using the Rosendaal method, 62% of patients had a TTR below 70%, while only 38% had a TTR greater than 70%. The mean TTR for the last eight months was 51.3% (median 48.8%, range 0-100%).

Crucially, no significant association was found between TTR and the occurrence of bleeding episodes (p=0.422). Similarly, no significant association was observed between TTR and strokes during the past three months (p=1.000). These results differ from meta-analyses and studies that indicate that higher TTR is associated with increased safety (reduced bleeding) of warfarin therapy, and lower TTR with a higher risk of both strokes and bleeding[21,24]. The ORBIT-AF registry also highlighted suboptimal TTR in AF patients[22]. The discrepancies in our findings may be attributed to the limitations of this study, such as its single-center nature and minimum sample size, which may not have provided sufficient power to detect these associations.

Table 2. Association between the stroke/TIA/Thromboembolism and CHA2DS2VASc score

Number of thrombotic episodes during past 3 months	CHA2DS2VASc score (0-6) and the number of individuals in each group							Significance
	0	1	2	3	4	5	6	
0	2	24	19	14	21	12	7	Fisher's exact test = 8.064
1	0	0	0	1	0	0	0	P value = 0.36

Discussion

In the studied Sri Lankan population, atrial fibrillation was predominantly observed in females and individuals over 65 years of age. The majority of patients resided in Colombo and its suburbs, suggesting that access to INR monitoring at NHSL was not a significant logistical challenge for most participants.

This study found no significant association between INR values and the type of bleeding episodes, nor did the HAS-BLED score predict major bleeding events in this population. Similarly, the CHA2DS2VASc score did not show a significant association with TIA/ stroke/ thromboembolism risk. A substantial proportion of INR values were found to be outside the therapeutic range and most patients had suboptimal TTR (<70%). Despite this, no association was observed between TTR and the occurrence of bleeding or thrombotic episodes. This study concluded that warfarin appears to be used safely for patients with non-valvular atrial fibrillation in this clinical setting.

A primary limitation of this study was its single-center design. While the calculated sample size was met, a multicenter study involving a larger patient cohort would provide more precise demographic data and allow for broader generalizability of the findings across Sri Lanka. Additionally, being a retrospective study, reliance on clinic records and patient interviews for bleeding and thrombotic episodes introduces potential for recall bias or incomplete documentation. A prospective study with a dedicated follow-up period would yield more accurate data.

Furthermore, the study was descriptive and lacked a control group, particularly one consisting of AF patients on DOACs. This absence made it challenging to directly compare the efficacy and safety of warfarin with DOACs, limiting definitive conclusions about the need for introducing DOACs in this setting. However, to definitively compare the safety and efficacy of warfarin with DOACs in the Sri Lankan context, future studies are strongly recommended. These studies should involve larger populations, multiple centers and ideally include a control group treated with DOACs to allow for robust comparative outcomes analysis. Such research is crucial for optimizing anti-coagulation strategies and informing healthcare policy regarding the introduction and utilization of newer anticoagulants in government hospitals in Sri Lanka.

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Disclosure of Conflict of Interests

The authors declare no conflict of interests related to this study.

References

1. Conen D. Epidemiology of atrial fibrillation. *Eur Heart J.* 2018; **39**(16): 1323-4.
2. Lip GY, Banerjee A, Boriani G, en Chiang C, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest.* 2018; **154**(5): 1121-201.
3. Association DwtscotEHR, Surgery EbtEAfC-T, Members ATF, Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *European Heart Journal.* 2010; **31**(19): 2369-429.
4. Appelboam R, Thomas EO. Warfarin and intracranial haemorrhage. *Blood reviews.* 2009; **23**(1): 1-9.
4. Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010; **138**(5): 1093-100.
5. Lip G, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost.* 2016; **14**(9): 1711-4.

6. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *European Heart Journal.* 2021; **42**(5): 373-498.
7. Stewart S, Hart CL, Hole DJ, McMurray JJV. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart.* 2001; **86**(5): 516-21.
8. Lokuhettige V, Chathuranga P, Kulathilake C, Ranasinghe N, Goonewardena S, Kumarapeli V. Relationship between HAS-BLED Score and Major Bleeding Events in Patients with Non-valvular Atrial Fibrillation on Warfarin: A Study at a Tertiary Care Teaching Hospital. *Asian Hematology Research Journal.* 2020: 27-34.
9. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *EP Europace.* 2012; **15**(4): 486-93.
10. Le Heuzey J-Y, Paziaud O, Piot O, Said MA, Copie X, Lavergne T, et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. *American Heart Journal.* 2004; **147**(1): 121-6.
11. Manawadu L, Fernando N. Processes driving ethnic segregation in cities: A case study of the city of Colombo, Sri Lanka. 2009.
12. Mathangasinghe Y, Ranatunga M, Ranasinghe P. The Knowledge and Adherence among Patients on Warfarin Therapy, the Anticoagulation Control and the Factors Associated with it: A Cross Sectional Study at Cardiology Clinic, National Hospital of Sri Lanka. General Sir John Kotelawala Defence University (KDU). 60.
13. Wallvik J, Själander A, Johansson L, Bjuhr Ö, Jansson J-H. Bleeding complications during warfarin treatment in primary healthcare centres compared with anticoagulation clinics. *Scandinavian Journal of Primary Health Care.* 2007; **25**(2): 123-8.
14. Breen AB, Vaskinn TE, Reikvam A, Skovlund E, Lislevand H, Madsen S. Warfarin treatment and bleeding. Tidsskrift for den Norske laegeforening: Tidsskrift for Praktisk Medicin, Ny Raekke. 2003; **123**(13-14): 1835-7.
15. Gallego P, Roldán V, Torregrosa JM, Gálvez J, Valdés M, Vicente V, et al. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. Circulation: *Arrhythmia and Electrophysiology.* 2012; **5**(2): 312-8.
16. Roldán V, Marín F, Fernández H, Manzano-Fernandez S, Gallego P, Vílchez JA, Valdés M, et al. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world" population with atrial fibrillation receiving anticoagulant therapy. *Chest.* 2013; **143**(1): 179-84.
17. Roldán V, Marín F, Manzano-Fernández S, Gallego P, Vílchez JA, Valdés M, et al. The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. *Journal of the American College of Cardiology.* 2013; **62**(23): 2199-204.
18. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *Jama.* 2015; **314**(10): 1030-8.
19. Okumura K, Inoue H, Atarashi H, Yamashita T, Tomita H, Origasa H, et al. Validation of CHA2DS2-VASc and HAS-BLED Scores in Japanese Patients With Nonvalvular Atrial Fibrillation – An Analysis of the J-RHYTHM Registry. *Circulation Journal.* 2014; **78**(7): 1593-9.
20. Vestergaard AS, Skjøth F, Larsen TB, Ehlers LH. The importance of mean time in therapeutic range for complication rates in warfarin therapy of patients with atrial fibrillation: A systematic review and meta-regression analysis. *PloS one.* 2017; **12**(11): e0188482.
21. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, Singer DE, Ansell J, Blanco RG, Gersh B, Mahaffey KW. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. *American Heart Journal.* 2015; **170**(1): 141-8.
22. Cotté FE, Benhaddi H, Duprat-Lomon I, Doble A, Marchant N, Letierce A, Huguet M. Vitamin K antagonist treatment in patients with atrial fibrillation and time in therapeutic range in four European countries. *Clinical Therapeutics.* 2014; **36**(9): 1160-8.
23. Nieuwlaat R, Connolly BJ, Hubers LM, Cuddy SM, Eikelboom JW, Yusuf S, Connolly SJ. Quality of individual INR control and the risk of stroke and bleeding events in atrial fibrillation patients: a nested case control analysis of the ACTIVE W study. *Thrombosis Research.* 2012; **129**(6): 715-9.